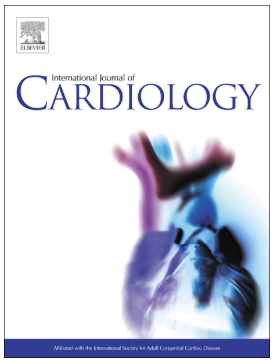

Effect of increased inspired oxygen on exercise performance in patients with heart failure and normal ejection fraction

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Effect of increased inspired oxygen on exercise performance in patients with heart failure and normal ejection fraction

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Abstract

Introduction: We investigated whether increased concentrations of inspired oxygen (Fi_{O_2}) affects exercise tolerance in patients with heart failure and normal ejection fraction (HeFNEF).

Methods: 46 patients (mean age 75 years (63% male) and median NTproBNP 1432 (interquartile range: 543-2378 ng/l)) with HeFNEF (defined as signs or symptoms of heart failure requiring treatment with diuretics, with a left ventricular ejection fraction of more than 45% by echocardiography and amino terminal pro brain natriuretic peptide (NTproBNP) >220 ng/l) completed three maximal incremental exercise tests with different Fi_{O_2} (21%, 28% and 40%) in random order. Fi_{O_2} was controlled by investigator but blinded to patients. The primary outcome was exercise time (ET).

Results: Increasing Fi_{O_2} significantly increased exercise time (522 ±180 seconds for 21% to 543 ±176 seconds, and 542 ±177 seconds, for 28% and 40%, respectively, P=0.04) with no difference in peak workload (57 ±25 W, 58 ±25 W and 57 ±25 W, for 21%, 28% and 40%, respectively, P=0.50). There was an increase in oxygen saturation but no change in peak heart rate with increasing Fi_{O_2}. Compared to patients with LVEF $\geq$ 50%, patients with LVEF between 45 and 49% had a significantly greater exercise time and peak workload. There was a correlation between the difference in exercise time between Fi_{O_2} 21% and 40% and age; but not with BMI, haemoglobin, creatinine or NTproBNP.

Conclusion: Increasing Fi_{O_2} during exertion leads to a small increase in exercise time in patients with HeFNEF.

Introduction

Epidemiological studies suggest that heart failure with normal ejection fraction (HeFNEF) accounts for almost 50% of patients with heart failure (HF), and its prevalence is increasing.[1,2,3] Compared to patients with heart failure and reduced ejection fraction (HeFREF), those with HeFNEF are usually older and have more comorbidities,[4] which plays a significant role in the development and/or worsening of HF symptoms and substantially contributes to the adverse prognosis of patients with HeFNEF. HeFNEF is a heterogeneous clinical syndrome which can be difficult to diagnose and treat.[4]

Clinical trials have failed to demonstrate that any pharmacological treatment improves outcomes for patients with HeFNEF.[5,6,7,8,9,10] However, another important aim of treatment is to alleviate symptoms and to improve wellbeing.[11] The clinical hallmark of HeFNEF is exertional breathlessness, at least partially due to an abnormal increase in left atrial pressure during exercise.[4] Reduction in delivery of oxygen to the periphery and myocardium might contribute to, and aggravate, breathlessness and fatigue.[4] Small trials suggest that increasing inspired oxygen concentration during exercise might prolong exercise time and improve symptoms in patients with HeFREF or pulmonary hypertension,[12,13,14] but the effect on patients with HeFNEF is unknown.

We aimed to assess the effects of increasing inspired oxygen fraction (FiO_2) on exercise capacity in patients with HeFNEF.

Methods

This was a single centre, randomised , single-blinded, cross-over trial in patients with HeFNEF. The research conforms to the Helsinki declaration. Ethics approval was granted by

an external research ethics committee. The trial was registered on the ClinicalTrials.gov website (Identifier: NCT02949531). All patients gave written informed consent.

Ambulatory patients older than 50 years of age attending a community heart failure clinic were considered for the study if they had had a clinical diagnosis of heart failure with a left ventricular ejection fraction (LVEF) by echocardiography $\geq$ 45% and a plasma concentration of amino terminal pro B type natriuretic peptide (NTproBNP) $\geq$ 220 ng/l.[15] Patients had to be taking a diuretic. Patients unable to exercise, and those who had severe mitral or aortic valve disease, haemoglobin < 100 g/l, estimated glomerular filtration rate <30 ml/min/1.73m^2), or severe chronic obstructive pulmonary disease (FEV_1 less than 50% predicted) were excluded from the study.

Exercise protocol

Patients undertook three maximal incremental exercise tests on a stationary cycle using a standardised exercise protocol. Patients cycled at 60 revolutions per minute starting from 0 watts for 4 minutes; subsequently, resistance increased by 10 watts/minute. Patients were encouraged to exercise to their maximum capacity. At the end of the exercise test, the reason for stopping and modified Borg score were recorded.

Inspired oxygen fraction (FiO_2) was administered at different concentrations (21%, 28% and 40%) in a random sequence which was computer generated. All three oxygen concentrations were delivered via a Venturi mask. This allowed the investigator to control the oxygen concentration administered whilst the patients and the technicians conducting the test were blinded to FiO_2. During the exercise test, blood pressure, oxygen saturation, heart rate and

rhythm were continuously monitored. The three exercise tests were conducted at approximately weekly intervals.

The primary endpoint was exercise time (ET; seconds). Secondary end points included: peak workload (watts), modified Borg score, peak heart rate (beats per minute), and peak arterial oxygen saturation (O_2 sat; percentage).

Statistical analysis

Categorical data are presented as number and percentages; normally distributed continuous data as mean ± standard deviation (SD) and non-normally distributed continuous variables as median and interquartile range.

Between-group means of the primary and secondary endpoints were compared using analysis of variance (ANOVA). The method uses 'least squares' to fit linear models. We used one-way ANOVA with repeated measures on dose-group. An underlying assumption of the F test is independence of observations. In a repeated measures design, this assumption is almost certainly violated (observations from the same subject are likely to be correlated). To overcome this, we used a correction factor (a number have been proposed in the literature) to the degrees-of-freedom for the F test. We chose one developed by Box which is conservative in a statistical sense (if significant by Box it will be significant by the rest).[16] Other assumptions of ANOVA were met. Paired t-tests were then used to compare the primary and secondary endpoints between exercise tests.

Sub-group analysis of the primary and secondary endpoints were pre-specified and used to explore the relation between age, haemoglobin, creatinine, NTproBNP, body mass index (BMI), sex, the use of a walking aid and heart rhythm (atrial fibrillation vs sinus rhythm) and

the end points. The current European Society of Cardiology guidelines on heart failure set an LVEF cut-off at 50% for diagnosing HeFNEF, so we re-analysed the results for patients above and below this LVEF cut-off.[11] Primary and secondary endpoints are shown in boxplots. All analyses were performed on SPSS (V 23.0) and Stata statistical computer packages. A statistical significance was assumed at $P<0.05$ (two tailed).

There were no missing values for exercise time so an analysis of missing data by multiple imputations was unnecessary.[17]

Results

Of the 50 patients enrolled, 46 patients completed the three visits, and 4 withdrew. (Supplementary Figure 1).The baseline characteristics of the 46 patients who completed the study are shown in table 1. Most patients were men, overweight and had NYHA class II symptoms. Compared to patients with LVEF $\geq$ 50%, patients with LVEF between 45 and 49% had a significantly higher NTproBNP and creatinine, and a lower haemoglobin.

Increasing FiO_2 led to an increase in exercise time of approximately 20 seconds (P=0.04). There was no dose response relation: exercise time was increased by the same amount during both tests with increased FiO_2 compared with 21% FiO_2. (Supplementary Table 1; Figure 1) Increasing FiO_2 had no effect peak workload (P=0.50) and modified Borg score (P=0.17). (Supplementary Table 1; Figure 1) There was no effect of increasing FiO_2 on heart rate during exercise (P=0.65), although arterial oxygen saturation throughout exercise was higher with increasing FiO_2 (P=0.03). (Supplementary Table 1)

Patients with LVEF $\geq$ 50% had a lower exercise time and peak workload than those with LVEF between 45-49%, but had a slightly greater increase in exercise time with the increase

in FiO_2 from 21% to 28%. (Table 2) There was no interaction between increasing FiO_2 and exercise capacity in any subgroup. (Supplementary Table 2) There was a positive correlation between the difference in exercise time between FiO_2 of 21% and 40% and age, but not with BMI, haemoglobin, creatinine or NTproBNP level. (Supplementary Table 3)

Discussion

We have found that in patients with HeFNEF, increasing oxygen concentration during exercise lead to a small increase in exercise time but had no effect on peak work load.

There are no previous trials of supplementary oxygen during exercise in patients with HeFNEF. Trials of oxygen supplementation during exercise in patients with heart failure with reduced ejection fraction (HeFREF) have yielded mixed results. Moore and colleagues reported a dose dependent increase in exercise time from 548 ±275 seconds on room air to 632 ±288 seconds with FiO_2 of 50% in 12 patients with HeFREF during resistance cycling on a stationary bike to maximum capacity (workload was increased by 15 W at 2-min intervals).[12] In contrast, Russell and colleagues found no effect of increasing FiO_2 to 60% on exercise time compared to 21% FiO_2 during symptom limiting resistance cycling on a stationary bike (2-minute resting period followed by increasing workloads of 25 W every 3 minutes) in 16 patients with LVEF <35%.[18] Restrick found no effect of oxygen delivered at 4 l/min on 6 minute walk test distance in 12 patients with stable chronic heart failure.[19] We studied 31 patients with HeFREF (mean LVEF 31%) and found that exercise time, maximal workload and maximal metabolic equivalent all increased significantly with increasing FiO_2 from 21%, to 28% and 40% FiO_2.[13] In a study of 22 patients with pulmonary hypertension (pulmonary arterial or chronic thrombo-embolic pulmonary hypertension), increasing FiO_2 to

50% approximately doubled exercise time (from 571 ± 443seconds to 1242 ± 514 seconds) and maximal work rate (113 ± 38 W to 132 ± 48 W).[14]

Why should increased FiO_2 improve exercise performance in patients with HeFREF, but not make a substantial difference in those with HeFNEF? Part of the explanation may be that HeFNEF is something of a diagnostic rag-bag. Extra-cardiac mechanisms may significantly contribute to impaired exercise tolerance in patients with HeFNEF. Those with HeFNEF tend to be older than those with HeFREF, are more likely to be overweight or obese and have chronic lung problems (and other comorbidities including anaemia).[20,21] Sarcopenia and loss of muscle bulk are common in older people and particularly in patients with HeFNEF.[22] Patients with HeFNEF are thus, perhaps, more likely to have conditions other than their heart failure that limits exercise, and hence oxygen is less likely to help their exercise performance.

In the present study, overall we found no relation between cardiac rhythm or plasma NTproBNP and exercise time. We found, perhaps paradoxically, that patients with LVEF between 45-49% had a longer ET than those with higher LVEF (≥50%), despite having a significantly greater plasma NTproBNP and lower haemoglobin level. Patients with LVEF between 45-49% may represent patients who truly have lower exercise capacity due to heart failure rather than those with LVEF >50% whose exercise performance might not be entirely related to the heart.[23]

The mechanisms causing exercise intolerance in patients with heart failure are complex.[24] In most stable ambulatory patients with HeFREF, haemodynamics at rest are not substantially impaired.[25] Major determinants of exercise capacity appear to lie in the periphery, with abnormal skeletal muscle performance being chiefly implicated. The situation may be different in patients with HeFNEF: again, haemodynamics at rest may be normal, but during exercise, there is a disproportionate increase in left atrial pressure,[26] which contributes to

symptoms and is associated with worse long term outcomes.[27] Trials in patients with HeFNEF which have exercise capacity as a primary endpoint may be likely to fail due to the heterogeneity of the condition.

Limitations

We only enrolled patients able to exercise. We also only included patients treated with a diuretic; this might have led to a population of patients with HeFNEF with a more severe disease profile.[28] Monitoring central haemodynamics during exercise testing might have added to the understanding of the causes of exercise intolerance in patients with HeFNEF.

We included some patients who had an LVEF 45% - 49% on echocardiography. According to the current ESC HF guidelines, these patients would fall into the newly introduced category of "heart failure with mid-range ejection fraction" (HFmrEF).[11] Such patients might represent a separate phenotype from patients with HeFNEF.

Conclusions

Increasing FiO_2 during exertion leads to a small increase in exercise time in patients with HeFNEF which is unlikely to be clinically significant.

Baseline characteristics of patients who completed the study

Baseline characteristics			
	All patients (N = 46)	**LVEF ≥ 50% (N= 29)**	**LVEF 45-49% (N= 17)**
Demographics			
Age (yrs)	75 (8)	76 (8)	75 (8)
Male Sex (%)	29 (63)	18 (62)	11 (65)
SBP (mmHg)	146 (23)	150 (23)	140 (23)
Heart rate (bpm)	69 (11)	70 (11)	68 (11)
BMI (kg/m^2)	31 (7)	32 (8)	31 (6)
Weight (kg)	90 (25)	91 (28)	91 (18)
NYHA function class			
I (%)	4 (9)	3 (10)	1 (6)
II (%)	37 (80)	23 (79)	14 (82)
III (%)	5 (11)	3 (10)	2 (12)
Medical history			
Hypertension (%)	28 (61)	19 (66)	9 (53)
Diabetes (%)	16 (35)	10 (35)	6 (35)
IHD (%)	20 (44)	13 (45)	7 (41)
Stroke (%)	3 (7)	3 (10)	0 (0)
#Asthma/ COPD (%)	10 (22)	8 (28)	2 (12)
Walking aids (%)	14 (30)	9 (31)	5 (29)
Blood test			
NTproBNP (ng/l)	1432 (543 – 2378)	1282 (443 – 2244)	2184 (1372 – 2501)*
Hb (g/l)	12.9 (1.7)	13.5 (1.7)	12.0 (1.5)*
Creatinine (µmol/l)	102 (80 – 137)	98 (75 – 125)	125 (95 – 155)*
ECG and ECHO			
Sinus rhythm (%)	21 (46)	15 (52)	6 (35)

Mean LVEF (%)	54 (7)	58 (5)	47 (1)*
LA size (cm)	4.3 (0.6)	4.2 (0.6)	4.5 (0.5)
IVS (cm)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)
Spirometry			
FCV % predicted	70 (17)	69 (21)	71 (12)
FEV1 % predicted	75 (20)	77 (23)	73 (17)
Medical therapy			
Beta blocker (%)	37 (80)	23 (79)	14 (82)
ACEi (%)	30 (65)	17 (59)	13 (77)
ARB (%)	10 (22)	7 (24)	3 (18)
Loop diuretics (%)	39 (89)	26 (90)	13 (77)
MRA (%)	23 (50)	13 (45)	10 (59)
Diuretic (%)	46 (100)	29 (100)	17 (100)
Digoxin (%)	8 (17)	8 (28)	0 (0)*
Statin (%)	34 (74)	22 (76)	12 (71)
Aspirin (%)	14 (30)	10 (35)	4 (24)
Anticoagulant (%)	28 (61)	16 (55)	12 (71)

Table 1: Baseline characteristics for all patients who completed three visits of the study and divided according to LVEF ($\geq$ 50% or between 45-49%). SBP: systolic blood pressure, BMI: body mass index; NYHA: New York Hear Association, IHD: ischaemic heart disease, COPD: chronic obstructive pulmonary disease, NTproBNP: Amino terminal pro brain natriuretic peptide, Hb: haemoglobin, ECG: electrocardiogram, ECHO: echocardiography, LVEF: left ventricular ejection fraction, LA: left atrial; IVS: interventricular septum, FCV: forced vital capacity, FEV1: forced expiratory volume in 1 second, ACEi: Angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, MRA: mineralocorticoid receptor antagonist. Categorical variables are expressed as number (percentage) and continuous variables are expressed as mean (standard deviation) or median (interquartile range) depending on distribution. P values significant (<0.05) between LVEF $\geq$ 50% and 45-49%. # those with severe COPD (FEV_1 less than 50% predicted) were excluded from the study.

Differences in the endpoint variables between LVEF ≥ 50% and LVEF between 45-49%

Variable	LVEF	21% FiO_2	28% FiO_2	40% FiO_2
Mean exercise time (seconds)	LVEF ≥50	482 (168)	509 (158)	504 (170)
	LVEF 45-49%	592 (184)	600 (194)	607 (173)
P value		0.04	0.09	0.05
Peak workload (watts)	LVEF ≥50	50 (19)	54 (19)	53 (20)
	LVEF 45-49%	68 (31)	65 (32)	66 (30)
P value		0.02	0.15	0.10
modified Borg score	LVEF ≥50	4.4 (1.9)	3.9 (1.4)	4.3 (2.0)
	LVEF 45-49%	4.6 (1.4)	4.7 (1.6)	4.7 (1.8)
P value		0.66	0.07	0.55
Peak heart rate (bpm)	LVEF ≥50	101 (18)	103 (18)	101 (23)
	LVEF 45-49%	110 (36)	110 (26)	111 (30)
P value		0.25	0.26	0.20
Peak oxygen saturations (%)	LVEF ≥50	96 (3)	97 (3)	98 (3)
	LVEF 45-49%	96 (5)	98 (3)	98 (3)
P value		0.25	0.52	0.93

Table 2: Changes in primary and secondary endpoints with the use of supplementary oxygen in patients with LVEF ≥50% or LVEF between 45-49%. FiO_2: concentration of inspired oxygen, LVEF: Left ventricular ejection fraction, bpm: beats per minute.

Highlights

1. The clinical hallmark of heart failure with normal ejection fraction (HeFNEF) is breathlessness
2. Increasing oxygen supplementation during exertion leads to a small increase in exercise time.
3. However this is unlikely to be clinically significant in patients with HeFNEF.
4. The mechanisms causing exercise intolerance in patients with HeFNEF are complex.

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Figure Legends

Figure 1: Increasing FiO_2 resulted in a small increased mean exercise time without a significant difference found between 28% and 40% as presented by arrows, but no significantly change mean peak workload and mean modified Borg score

Supplementary Figure 1: Total number of patients consented and completed all three visits of the study

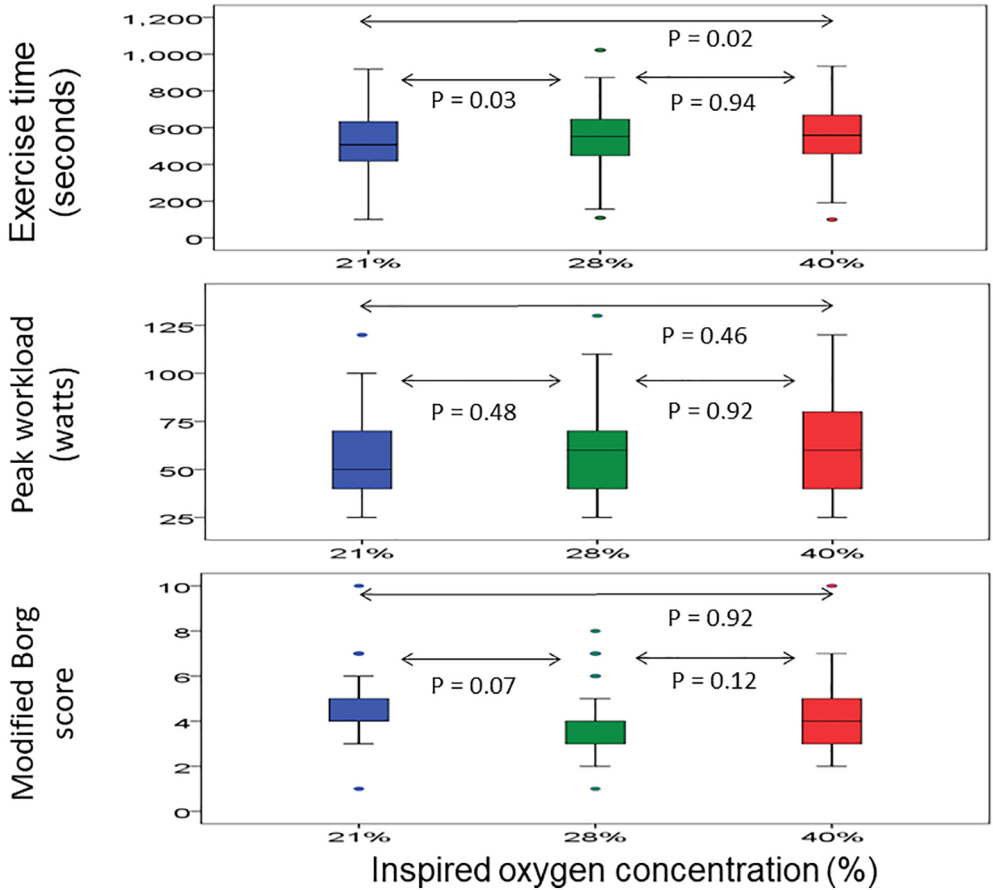
Exercise time (seconds)
1,200
1,000
800
600
400
200
0
P = 0.02
P = 0.03
P = 0.94
21%
28%
40%
Peak workload (watts)
125
100
75
50
25
P = 0.46
P = 0.48
P = 0.92
21%
28%
40%
Modified Borg score
10
8
6
4
2
0
P = 0.92
P = 0.07
P = 0.12
21%
28%
40%
Inspired oxygen concentration (%)

Figure 1

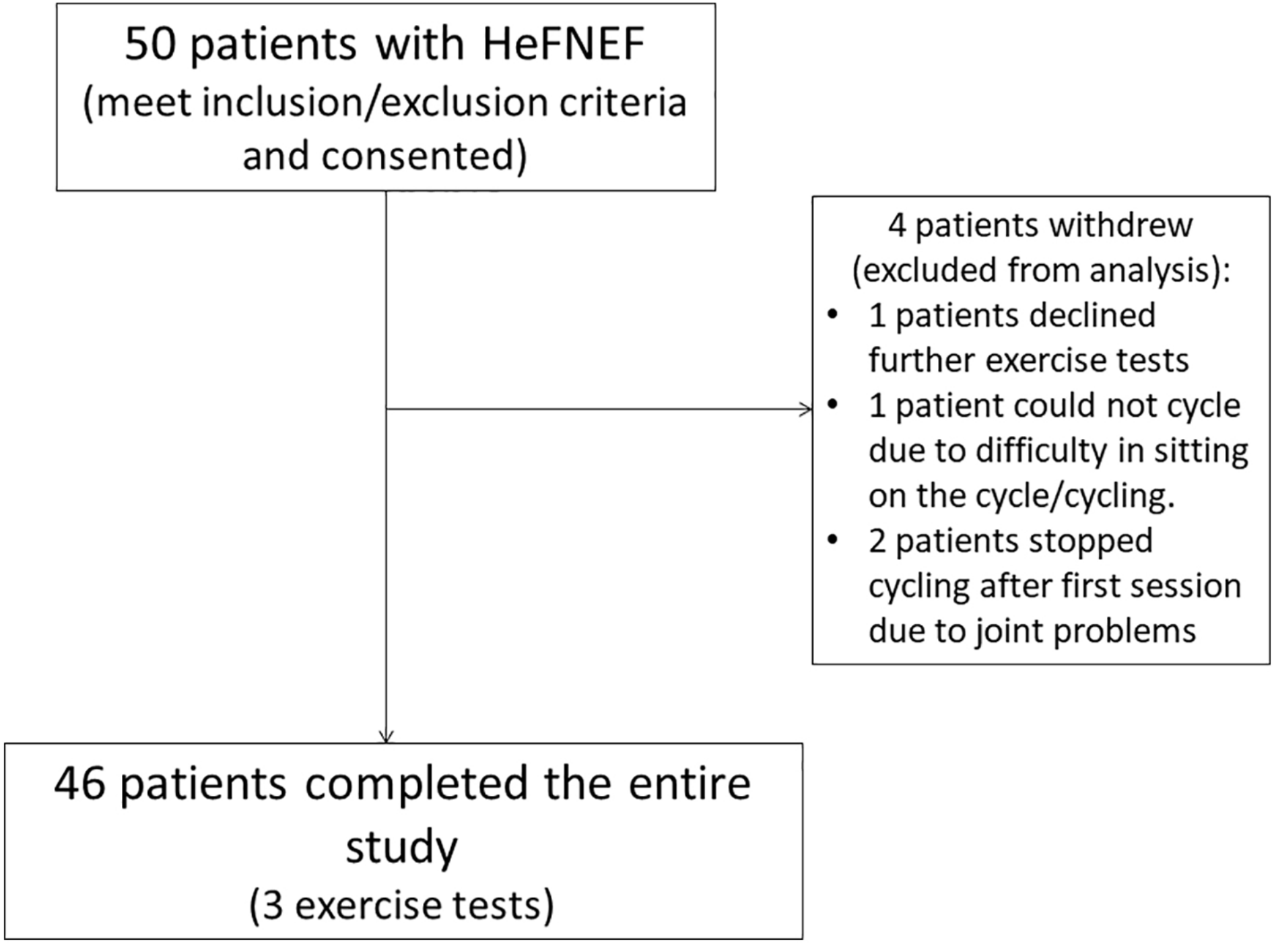
50 patients with HeFNEF
(meet inclusion/exclusion criteria and consented)
4 patients withdrew (excluded from analysis):
• 1 patients declined further exercise tests
• 1 patient could not cycle due to difficulty in sitting on the cycle/cycling.
• 2 patients stopped cycling after first session due to joint problems
46 patients completed the entire study
(3 exercise tests)

Figure 2